



# Biological Sexual Differences in Covid-19 Infection

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### Review Article

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## Introduction

The Coronavirus disease (COVID-19), formerly known as novel Coronavirus pneumonia, NCP, is a potentially deadly illness induced by a novel pathogenic coronavirus, formerly named as novel Coronavirus, 2019-nCoV (now named Severe Acute Respiratory Syndrome Coronavirus 2, SARS-CoV-2). SARS-CoV-2 is a type of  $\beta$ -coronavirus, of the subgenus sarbecovirus and subfamily Orthocoronavirinae, which is a type of enveloped non-segmented positive-sense RNA virus [1]. Coronaviruses (CoV) are subdivided into four genera namely;  $\alpha$ -/  $\beta$ -/ $\gamma$ -/ $\delta$ -CoV. The  $\alpha$ - and  $\beta$ -CoV infect mammals, while  $\gamma$ - and  $\delta$ -CoV infect birds. The virus originated from Wuhan, Hubei province, China in December 2019. The virus has since spread across all continents, making the disease to be classified as a pandemic as a result of the widespread. The symptoms associated with COVID-19 can range from mild to severe illness or could also be asymptomatic (or showing no symptoms). Apart from the 2019-nCoV, other coronavirus species have been identified; the first Severe Acute Respiratory Syndrome Coronavirus SARS-CoV, emerged in 2002 in China [2], and Middle East respiratory syndrome coronavirus, MERS-CoV, in 2012, with both detected to have been hosted by bats and some other animals and eventually transmitted to humans and can cause light to severe respiratory diseases respectively in humans [3]. In facilitation of proper and intensive care, early identification of the risk factors for critical conditions associated with the infection is urgently necessary as to also identify the defining clinical and epidemiological characteristics of the condition with greater precision. On February 23, 2020, the Chinese health authority announced that the total number of confirmed cases of people infected on the Chinese mainland had reached 76,936, and that 2,442 people had died of the disease then. Majority of the deceased patients were old and about two-thirds were males [4],

leading to concerns on whether men are more susceptible to getting infected and dying as a result of COVID-19. A study suggested that the infection more likely affects older males with comorbidities, and could further lead to severe and fatal respiratory diseases [5], and another study suggested that the percentage of men is group is greater than that of women among those affected [6], although the infection is independent of age differences in transmission. As of 13 April, 2020, a total of 747,546 people had been confirmed to be infected via case reporting forms (CRFs) received from 113 countries, territories and areas across five different WHO regions and three international conveyances [7].

## Epidemiology of Covid-19

Coronavirus is one of the major pathogens that primarily target the human respiratory system. Former outbreaks of CoVs such as the SARS-CoV and the MERS-CoV have been previously labelled as infections of great public health threat [8]. In December 2019, a cluster of patients was admitted to hospitals with an initial diagnosis of pneumonia of an unknown etiology. The widespread of the infection broke out first in Wuhan, China, since 12 December 2019, believed then to be related to a seafood market. Several studies have since then proposed that the potential reservoir of the SARS-CoV-2 may be bats [9,10]. Even as though bats have been widely dubbed as the natural reservoir of the virus as well as some other CoVs, including SARS-CoV-like and MERSCoV-like viruses [11-13], there still is no clear evidence that the SARS-CoV-2 originated from the seafood market.

The SARS-CoV-2 possess almost the same contents in genome with SARS-CoV, specific research have shown that the particular genome sequence of SARS-CoV-2 is about 96% identical to a certain bat CoV RaTG13, and that it shares over 79% identity to SARS-CoV. Based on results obtained

from the genome sequencing and evolutionary analysis of the virus, it has been widely suspected that bats are the natural hosts, and the virus might be transmitted from them to humans via unknown intermediate hosts. It is now clear that SARS-CoV-2 could use angiotensin-converting enzyme 2 (ACE2), the same receptor as SARS-CoV [14], to infect humans, even the Patients infected by 2019-nCoV and SARS-CoV show comparable clinical features. Currently the mode of SARS-CoV-2 transmission is via human-human contact, directly or indirectly. One can easily get infected by coming in close contact with a person already infected with the disease. This implies that the disease spreads primarily from person to person. One can also become infected via respiratory droplets deposited when an infected person coughs, sneezes, or talks, or even by touching a surface or object that has the virus on it, and then by touching the mouth, nose, or eyes thereafter. Studies have estimated that the basic reproduction number,  $R_0$ , of SARS-CoV-2 is around 2.2 [15], or between the range of 1.4 to 6.5 [16], and familial clusters of pneumonia [17], outbreaks buttress the evidence of increasingly rising human-to-human transmission leading to widespread of COVID-19.

Studies have shown that the bat CoV and human SARS-CoV-2 might have emerged from the same ancestor, as COVID-19 genome was sequenced and analyzed throughout the genome to Bat CoV RaTG13 and it showed 96.2% overall genome sequence identity [14], although bats are sold in the seafood market it's said to have emerged from Wu [18]. Additional research have also showed alignment of protein sequences and the phylogenetic analysis [16], have showed that similar residues of receptor were observed in many species, which tend to expose other animals such as turtles and pangolin, as well as snacks as probable intermediate hosts [19]. Human-to-human transmission of SARS-CoV-2 occurs usually between people who often come in close contact daily such as family members, relatives and friends who have intimately contacted with patients or incubation carriers. Conversely, the transmission of SARS-CoV and MERS-CoV is said to occur through nosocomial transmission [19]. The most common route of infection in MERS-CoV cases was transmission between patients (62–79%), and infections of healthcare workers in 33–42% of SARS cases [20,21], whereas the main route of SARS-CoV-2 transmission is thought to be via direct contact with intermediate host animals or consumption of wild animals [19].

The SARS-CoV-2 upon contact with living tissue goes through an incubation period and the symptoms of the COVID-19 infection begin to appear at approximately 5.2 days [22]. The period from the onset of the symptoms to death ranged from 6 to 41 days with a median of 14 days [23], and is critically dependent on the age, and the status of the immune

system of the patient. Studies have showed this period to be shorter among patients above 70 of age compared with those below that age [23]. At the onset of COVID-19 infection, the most common noticeable symptoms are fever, dry cough, and general fatigue, though other symptoms such as production of sputum, headache, haemoptysis, diarrhoea, dyspnoea, and lymphopenia may be present [23-26]. A chest CT scan of an infected person, initially presented as pneumonia, showed abnormal features such as RNAemia, acute respiratory distress syndrome, acute cardiac injury, and incidence of grand-glass opacities in subpleural regions of both lungs that led to death [25,27]. These ground-glass opacities are believed to have induced both systemic and localized immune response leading to increased inflammation.

### Prevalence of Covid-19 Infection on Males and Females

Older age and male gender have both been labelled as potential risk factors for worse outcome in patients with COVID. Studies have shown that men and women have the same susceptibility to SARS-CoV-2, although men may be more susceptible to have higher severity and mortality independent of age and susceptibility. The data to back these up might be inconclusive though, as majority of the earlier reported cases published failed to identify the particular genders. As a result of this, conclusions have been made based on the recent findings and specific case studies.

On February 23, 2020, the Chinese health authority announced that the total number of confirmed cases of people infected on the Chinese mainland had reached 76,936, and that 2,442 people had died of the disease then. Majority of the deceased patients were old and about two-thirds were males [4], leading to concerns on whether men are more susceptible to getting infected and dying as a result of COVID-19. A particular study using a case series of 43 infected patients showed a large number of the patients had at least one underlying disorder (i.e., hypertension, diabetes, cardiovascular diseases and chronic lung diseases) and compared the ages, symptoms and comorbidities between men and women. The men presented a higher level of hemoglobin, presumably due to red blood cells count, and also the male patients had elevated levels of serum creatinine, white blood cells and neutrophils [28].

The World Health Organization (WHO) published that a total of 747,546 cases of confirmed COVID infection were confirmed on 13<sup>th</sup> of April, 2020. These cases were documented via case reporting forms (CRFs) received from 113 countries, territories and areas across five different WHO regions and three international conveyances. The number of cases with a CRF accounts for 44.0% of the confirmed cases

reported globally as of 13 April 10 AM. 42.3% of the CRFs were reported from Europe, 55.6% from American region, 1.4% from the Western Pacific Region, 0.6% from Eastern Mediterranean Region, 0.02% from South-East Asia Region, and none from the Africa Region. It also stated that the United States of America, Italy and Germany accounted for 74% of cases which were documented with CRFs in the database and so the data should not be considered as representative of all globally confirmed COVID-19 cases [29]. Precisely 95.9% of the CRFs showed information on age and sex and the sex ratio (male to female) among the confirmed cases was 1.03:1, and the median age was 51 (interquartile range, IQR: 36-65) years. Median age for males, was 52 (IQR 37-65) years, while that of females was 50 (IQR 35-64) years. Eventually, the sex ratio varied significantly with age in all ranges except 10-19 years; the largest sex ratios (male to female) are observed amongst the 0-9 year (1.16), 60-69 year (1.27:1), and 70-79 year (1.34:1) age groups. Conversely, the lowest sex ratios (i.e. those showing more females than males) are found in the 20-29 year (0.85:1) and 80 years and over (0.78:1) age groups. When cases reported from the United States, Germany and Italy are excluded, the overall sex ratio changes to 0.95:1 (more females than males amongst the cases), while there remains an excess of males in the 0-9, 60-69 and 70-79 year age groups [29].

In another live study that provides insight to the proportion of males to females in COVID-19 infection, a gender-based reproductive health initiative known as Global Health 50/50 project monitored a study on 18 different countries, and the resultant reports showed similar numbers of COVID-19 cases in men and women, except in Pakistan where 72% of cases were male [30], although there are doubts about the accuracy in number of women. The unsolved implication this is that in all countries that report death rates by sex, men diagnosed with COVID-19 are the ones that are more likely to die. In the same report, the male/female ratio of deaths among confirmed cases ranges from 1.1 in Iran to 2.1 in Denmark and Greece and the ratio also tends to be higher in older people: it is consistently above 2 in people aged 60 years and over, and more than 3 among men and women aged 70-79 years in Italy. This shows there's a relative correlation between the age and sex and the role they both play in manifestation of the symptoms and death rates. Various reports also showed that men had worse outcomes of illness from Karlberg J, Chong DS, and Lai WY [31], and higher risk of death from Chen [32], Another report also showed that men with COVID-19 in the United Kingdom require intensive care the more and are more prone to death. The UK Intensive Care and National Audit Research Centre (ICNARC) recently published a report on the first 2,249 patients admitted to intensive care in the UK with COVID-19 infection, with 775 of those patients with full data. Of those

with full data, men with COVID-19 were more prone to death than women (53.2% v. 37.5%) and were larger in proportion among those needing mechanical ventilation (73% v. 27%) and basic respiratory support (71% v. 29%). ICNARC were also able to compare COVID-19 admissions with their data on viral pneumonia admissions from 2017-2019. This showed that 70% of COVID-19 admissions were males versus 54% of those with pneumonias caused by other viruses, ICNARC [33].

There is a particular theory which suggests the genetic differences between males and females in regards to the immune system. In the whole genome, the X chromosome is said to possess the largest number of immune-related genes [34]. Females with their double(XX) chromosome, tend to own a double portion of important immune genes, compared to the single copy possessed in XY men. Although this is only assumed and has not been scientifically proven in relation to COVID, it is believed that the increased number of those immunity genes in females gives them an edge to tackle via both the general reaction to infection (the innate immunity) and also to the more specific response to microbes including antibody formation (adaptive immunity) [35]. Thus, one can say females' immune systems are generally more active and responsive to infections than males. Another theory suggests that the higher degree of manifestation in males owes to tobacco smoking, using China as a study because about 50% of men in China smoke compared to only just 2% women who does because is not considered acceptable for women to smoke. Combined results from five studies showed that smokers were 1.4 times more likely than non-smokers to have severe symptoms of COVID-19 and 2.4 times more likely to be admitted to an intensive care unit, need mechanical ventilation or eventually die [36,37].

## Conclusion

Old age and male gender are believed to both be risk factors for worse outcome in patients with COVID. While men and women are equally susceptible to SARS-CoV-2, men may be more prone to have higher severity and mortality independent of age and susceptibility. Genetic variation and immunity strength as well as smoking tobacco have been highlighted as potential causative factors. Even though most reports have assumed that the effects of COVID-19 infection on males is more severe than that of females, and that the men are more prone to death as a result due to the estimated ratio gathered from reports of countries via CRFs, the assumptions are scientifically inconclusive, as there hasn't been any research to verify scientifically till date. Besides this, lots of other factors such as social and environmental factors, exposure to certain chemicals, age and underlying diseases could be as well be responsible rather than assuming it is due

to the genetic and biological sexual differences of males and females.

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